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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US99/17543 (22) International Filing Date: 2 August 1999 (02.08.99) (30) Priority Data: 09/127,920 3 August 1998 (03.08.98) US (71) Applicant: INSITE VISION, INCORPORATED [US/US]; 965 Atlantic Avenue, Alameda, CA 94588 (US). (72) Inventors: BOWMAN, Lyle, M.; 5135 Mount Tam Circle, Pleasant, CA 94588 (US). PFEIFFER, James, F.; 2369 Thackery Avenue, Oakland, CA 94611 (US). CLARK, Leslie, A.; 829 #B Lincoln Avenue, Alameda, CA 94501 (US). HECKER, Karl, I.; 400 Hurricane Road, Keene, NH 03431-2161 (US). (74) Agents: FREED, Joel, M. et al.; Howrey & Simon, 1299 Pennsylvania Avenue, N.W., Box 34, Washington, DC 20004-2402 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: METHODS OF OPHTHALMIC ADMINISTRATION (57) Abstract Intrasccleral injection of a therapeutic or diagnostic material at a location overlying the retina provides a minimally invasive technique for delivering the agent to the posterior segment of the eye. The procedure also allows for close proximity of the material to the targeted site and can be effectively used to treat conditions associated with the posterior segment of the eye, including macular degeneration, vein occlusion, and diabetic retinopathy. The sclera can be used to hold a depot of the material such as for sustained released or as a conduit for propelling material through whereby the material is delivered immediately to the underlying tissues but without physically penetrating the sclera with an instrument or otherwise unreasonably traumatizing the eye. 		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/17543

A. CLASSIFICATION OF SUBJECT MATTER

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K38/55 A61K38/46 A61K48/00 A61K39/395
A61P21/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y DATABASE MEDLINE 'Online!
US NATIONAL LIBRARY OF MEDICINE (NLM),
BETHESDA, MD, US
VERBEEK A M ET AL: "Recurrent intrascleral
cyst after strabismus surgery."
retrieved from STN
Database accession no. 97024955
XP002130928
abstract
& GRAEFES ARCHIVE FOR CLINICAL AND
EXPERIMENTAL OPHTHALMOLOGY, (1996 AUG) 234
SUPPL 1 S229-31.

1-41

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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8 document member of the same patent family

Date of the actual completion of the international search

18 February 2000

Date of mailing of the international search report

02/03/2000

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 09838 A (CELTRIX PHARMACEUTICALS, INC.) 4 April 1996 (1996-04-04) page 6, line 20 -page 7, line 31; claims 1,6,15 page 15, line 1 -page 20, line 33 page 22, line 6 - line 8	1-41
Y	WO 92 08406 A (THE UNIVERSITY OF ROCHESTER) 29 May 1992 (1992-05-29) cited in the application page 1, line 5 - line 12; claims 9-11; figure 5 page 3, line 9 - line 15 page 5, line 13 - line 16	1-41
Y	WO 97 41844 A (ALCON LABORATORIES) 13 November 1997 (1997-11-13) page 5, line 4 - line 5; claims page 20, line 10 -page 21, line 15 page 23, line 1 - line 12	1-41

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/17543

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
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3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/17543

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9609838	A	04-04-1996	AU 3584895 A	19-04-1996
WO 9208406	A	29-05-1992	US 5273530 A	28-12-1993
			AU 9062891 A	11-06-1992
			CA 2096006 A	15-05-1992
			EP 0557445 A	01-09-1993
			JP 6505647 T	30-06-1994
			US 5409457 A	25-04-1995
WO 9741844	A	13-11-1997	AU 2438297 A	26-11-1997

METHODS OF OPHTHALMIC ADMINISTRATION

BACKGROUND OF THE INVENTION

1. Field of the Invention

5 The present invention relates to methods of ophthalmic administration. Specifically, the methods relate to intrascleral injection of therapeutic or diagnostic materials.

2. Description of the Related Art

10 Delivering therapeutic or diagnostic agents to the posterior segment of the eye, especially to the retina, macula, etc., poses several challenges. Topical instillation of an agent to the front of the eye such as by eye drops, generally provides low amounts of the agent (including none) to the posterior portion of the eye, due in part to poor diffusion through the various layers as well as the natural clearing processes encountered.

15 Providing effective amounts of an agent to, for example, the retina via topical instillation is generally not possible given the distance and number of layers between the deposit site of the agent and the site to be treated. Another potential shortcoming with topical instillation is that the composition tends to be quickly removed from the eye by tears and other natural clearing processes. The resulting short duration of contact can further limit the

20 likelihood of an appreciable amount of the agent reaching the posterior segment.

 Conversely, systemic delivery of an agent to the posterior segment of the eye such as by oral administration, is limited by the blood-retinal barrier. The barrier limits the size and amount of agents that can reach the choroid and retina. Moreover, because the agent is systemically delivered, the dosage is limited so as not to provide a toxic dose

25 of the agent to other parts of the body. This is especially a concern in treating chronic disorders where a long term dosing regimen is typically required. For this reason,

overcoming the barrier by administering higher doses of the agent is usually not a practical alternative. Likewise, the risk of side effects is increased with systemic delivery.

Other proposals for delivering agents to the eye include the use of inserts and implants which release the agent over time onto or into the eye. An insert, as used in
5 this application, is a device inserted over the eye, such as on the conjunctival layer, and generally comprises a polymer matrix containing an active agent. The agent that is released from the insert can diffuse through the sclera and into the eye. While sustained or long term agent contact with the eye can be achieved by this method, little if any of the agent reaches the posterior segment of the eye for much the same reasons as topical
10 instillation. Implants are devices similar to inserts but they are surgically placed within the eye. Accordingly, implants bring the risk of infection and other problems due to its more invasive nature.

For example, U.S. patent 4,863,457 to Lee relates to an implant having a stem and base wherein the stem releases a drug and is positioned to extend into a canal,
15 passageway, or orifice of the eye. The implant is taught to serve two functions: internal delivery of drug and mechanical prevention of passageway closure. The drawings illustrate placing the base of the implant in the subconjunctival space, or within the sclera itself, with the stem extending into the anterior chamber. The implant is taught to be especially useful in post-operative glaucoma patients as the drugs released can suppress
20 scar tissue around the stem while the stem structure helps to maintain a passageway from the anterior chamber to Schlemm's canal. In this way, the implant is taught to ensure continued drainage of the aqueous humor from the anterior chamber and prevent a recurrence of the pressure buildup caused by glaucoma.

However, this implant is directed to treating the anterior chamber and not
25 the posterior segment of the eye. Indeed, the option of inserting the implant into the sclera is problematic if attempted in the posterior segment of the eye. Here, partially

cutting the sclera where it overlies the retina and inserting the base and stem of the implant therein, raises the risk of retinal detachment and choroidal hemorrhage. Only in the front of the eye, where the sclera does not overlie the retina and the vasculature of the choroid is low, can the partial thickness sclera flap technique be practically performed.

- 5 Accordingly, the design and placement of this implant is not effective for delivering an agent to the posterior portion of the eye.

U.S. patent 5,707,643 to Ogura *et al.* relates to a biodegradable scleral plug that is inserted through an incision in the sclera into the vitreous body. The plug releases a drug into the vitreous body for treating the retina. The path of the plug is not, however, indicated. Assumedly, the plug would extend through the avascular region of the pars plana so as not to rupture any significant blood vessels or the retina. The drug will be applied to the entire retina by diffusion through the vitreous body, thus precluding the ability to provide a more concentrated application of the drug to one portion of the retina. Also, the invasive nature of the plug brings various risks including the risk of infection.

- 15 U.S. patent 5,443,505 to Wong *et al.* relates to implants that are taught to deliver drug to a localized site. The implants are typically placed in the suprachoroidal space over an avascular region of the eye such as the pars plana or a surgically induced avascular region. Another embodiment involves forming a partial thickness scleral flap over an avascular region, inserting the implant onto the remaining scleral bed, optionally with holes therein, and suturing closed the flap. The drug diffuses into the vitreous region and the intraocular structure. Locating the implant close to the back of the eye is apparently not possible as the region would not be avascular, unless surgery is performed to make an avascular region. Such removal is normally undesirable since vision loss will
- 20 be induced.
- 25

Another delivery approach is direct injection. For the posterior segment of the eye, an intravitreal injection has been used to deliver drugs into the vitreous body. U.S. patent 5,632,984 to Wong *et al.* relates to the treatment of macular degeneration with various drugs by intraocular injection. The drugs are preferably injected as

5 microcapsules. The intraocular injection into the posterior segment is taught to allow diffusion of the drug throughout the vitreous, the entire retina, the choroid and the opposing sclera. Similarly, U.S. patent 5,770,589 to Billson *et al.* relates to treating macular degeneration by intravitreally injecting an anti-inflammatory into the vitreous humor. These invasive injections are normally administered through the pars plana in

10 order to minimize the damage to the eye. While drug is delivered to the posterior segment, it is not specifically administered to a target area such as the macula, but rather is supplied to the entire posterior segment. Additionally, the procedure has a high risk of infection and retinal detachment and has restricted use.

U.S. patent 5,767,079 to Glaser *et al.* relates to the treatment of

15 ophthalmic disorders including macular holes and macular degeneration, by administration of TGF- β . The method of administration varies depending upon the nature and location of the pathology. The patent contemplates placing an effective amount of the growth factor on the ophthalmic abnormality. In treating the macula and retina, the examples teach that a surgical procedure involving a core vitrectomy or a complete pars plana vitrectomy is

20 performed before the growth factor can be directly applied. The patent does mention the possible use of, *inter alia*, an intrascleral injection. However, no specifics are given about such a procedure, nor is such a procedure well known in the art. Presumably, the patentee intended either administration to the sclera on the anterior segment of the eye at an avascular region or administration to the sclera behind the retina via a surgical procedure

25 through the vitreous body, retina, and choroid. The former method will not provide a large amount of drug to the posterior segment, as discussed above with regard to topical

instillation and implants. The latter method is a dramatic, highly invasive, technique that would be suitable only where partial vision loss has already occurred or was imminently threatened. Such a procedure carries a high risk of infection or retinal detachment as well as loss of vision and clearly is problematic for chronic administration.

5 U.S. patent 5,273,530 to del Cerro *et al.* relates to the intraretinal delivery and withdrawal of samples and a device therefor. Unlike direct intraocular injection techniques, the method disclosed in this patent avoids the use of a pars plana incision and instead uses an insertion path around the exterior of the orbit. The device, having a curved handle and a tip with collar, allows a cannula to be inserted through the posterior
10 sclera and down into the subretinal space without passing through the vitreous body. The collar is stated to regulate the penetration to the desired depth. The method is basically directed to supplying cells to and/or withdrawing samples from the subretinal space. However, the device is taught to be adjustable to any part of the eye including the scleral area, the choroidal area, the subretinal area, the retinal area and the vitreous area. In use,
15 the disclosed subretinal delivery method presents a significant risk of causing choroidal hemorrhaging. It should be noted that although the approximate location of the cannula can be observed through a slit lamp by tinting, the penetration of the cannula through the sclera and choroid can not be seen until the tip of the cannula penetrates the retinal surface.

20 The above methods show that delivering agents to the posterior segment of the eye, especially the back of the eye at the retina, macula, etc., is difficult. This region of the eye is isolated by both the anterior segment and the blood-retinal barrier. The techniques which are relatively easy to apply (topical instillation, oral administration) generally do not deliver a sufficient amount of the agent to the posterior segment and/or
25 present toxicity or side effect problems. In contrast, techniques that deliver effective amounts (intravitreal injection) are complicated, invasive procedures that subject the

patient to the risk of infection, retinal detachment, and further vision or eye damage. A minimally invasive method for delivering agents to the posterior segment of the eye would be of great benefit.

5

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for administering agents to the eye.

It is another object of the present invention to provide a method for administering agents to the eye that is minimally invasive.

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Preferred forms of the invention contemplated accomplish at least one of the above objects. One embodiment of the invention is a method of intrascleral injection, which comprises injecting into the scleral layer of an eye through a location on the exterior surface of the sclera which overlies retinal tissue an effective amount of a therapeutic or diagnostic material. Depending on the injection conditions, the material will (1) form a depot within the scleral layer and diffuse into the underlying tissue layers such as the choroid and/or retina, (2) be propelled through the scleral layer and into the underlying layers, or (3) a combination of both (1) and (2). By entering the sclera from the external side, the method avoids the invasiveness of the intravitreal injection technique, thereby reducing the risk of infection and allowing a regimen of treatments to be given throughout the year, if needed. Also, because the sclera moves with the entire eye including the retina, the site of deposit on the sclera will map to the corresponding point on the underlying retina, even as the eye moves within the eye socket. This means that site specific delivery can be achieved and maintained. Thus, by depositing material into the sclera at a site overlying the macula, the material will be easily delivered to the macula and surrounding tissues.

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The injection procedure is not particularly limited and embraces the use of a cannula or needle as well as needle-less particle/solution techniques. In a preferred embodiment, a cannula is inserted into the sclera in a rotational direction relative to the eye and not orthogonal to the surface of the sclera. By angling the cannula insertion into the sclera, the risk of accidentally perforating the sclera and causing damage to the underlying tissue (choroid and retina) or hemorrhaging can be reduced or eliminated.

The present invention allows the delivery of a variety of agents to the posterior segment of the eye whenever such delivery would be desirable, including treating conditions of the posterior or anterior segments and diagnosing various conditions.

10

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates an eye having a cannula inserted into the scleral in accordance with one embodiment of the present invention.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention involves injecting a material into the sclera of an eye. The eye can be of any vertebrate animal including human and non-human mammals. The sclera is a thin, avascular layer, comprised of a highly ordered collagen network, that surrounds most of the vertebrate eye. The cornea replaces the sclera in the front of the eye, with the transition from sclera to cornea occurring at the limbus. Because the sclera is avascular, there is essentially no risk of hemorrhaging after an injection therein and the injected material is not rapidly removed or "cleared" from the eye. Thus the sclera can be effectively utilized in the present invention as a natural storage depot. Further, because of the fibrous and inelastic nature of the sclera, it can be used as a diffuser screen through which the material is propelled. This allows for the rapid delivery of the material to the underlying tissue(s). In any event, injecting the material into the scleral layer, either so it

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can diffuse out or so it is propelled out, provides for a minimally invasive technique for providing the material to ocular tissues in the posterior segment of the eye.

The material can be placed within the sclera by any suitable injection technique including cannular and non-cannular techniques. Typically a cannula is inserted
5 into the sclera and the therapeutic or diagnostic material is then injected through the cannula and into the scleral layer. In more detail, an embodiment of the present invention using a cannula is described below with reference to fig. 1.

Eye 10 (not drawn to scale) can be divided into an anterior segment 20 and posterior segment 30 with an equator 40. Sclera 11 covers the outside of the eye around
10 the posterior segment and part of the anterior segment while cornea 21 covers the outer part of the remainder of the anterior segment. Underlying the sclera is choroid 12 and retina 13. A cannula 50 (shown here as a needle with a beveled terminal end) has been inserted into the sclera from a location on the external (or outer) surface of the sclera that overlies the retina. In this inserted position, conveying material through cannula 50 will
15 result in injecting the material into the scleral layer. The cannula has been inserted in a substantially rotational direction meaning that the insertion path into the sclera generally points around the eye and not into the center of the eye. This is a preferred embodiment because it decreases the risk of accidentally penetrating through the sclera and into the choroid or retina. Obviously, inserting a cannula, especially a sharpened or beveled
20 cannula, into the vascular choroid or light sensitive retina can cause serious injury to these layers with resulting vision impairment. Generally insertion of the cannula in a "substantially rotational direction" will be performed at an insertion angle of less than about 60 degrees; the "insertion angle" being defined by the angle formed between the tangent to the sclera at the external point of entry and the insertion path of the cannula
25 into the sclera (or in the case of a curved cannula, the tangent to the curved cannula insertion path at the entry point into the sclera). Preferably the insertion angle is less than

50, more preferably from about 20 to about 40 degrees. In one embodiment the insertion angle is about 30 degrees.

In a preferred embodiment, the cannula is inserted in an orientation to the sclera such that it must exit the sclera, if at all, through another location on the exterior surface of the sclera: hereinafter a "fail safe orientation." This can be accomplished, for example, by inserting a straight cannula at a sufficiently low insertion angle. Because the sclera is curved, the cannula can be angled so as to travel on a path that is tangential to a point on the curving interior surface layer of the sclera. At all insertion angles lower than this tangential angle, the closest the cannula will come to the inner surface of the sclera is a point above the tangent point. Further extending the cannula beyond this point will bring the leading end of the cannula further away from the interior surface of the sclera and closer to the exterior surface of the sclera. Thus, the cannula will miss perforating the interior surface of the sclera no matter how far the cannula is extended. This provides a safer injection technique in that if the cannula is inserted "too far," the result is only that the injected material will not go into the sclera as intended, but instead will be deposited on the exterior of the sclera. Such injections into the external part of the eye should have no deleterious effect. Orienting the cannula, whether curved or straight, such that it enters the sclera from the exterior surface thereof and must exit the sclera, if at all, also through the exterior surface and not through the inner surface of the sclera, significantly reduces the risk of accidentally damaging the choroid or retina.

Inserting the cannula in a substantially rotational direction also allows for increased insertion distances of the cannula into the sclera which can increase the hydrodynamic seal between the cannula and the scleral tissue. A poor hydrodynamic seal can lead to the material leaking out of the sclera along the sides of the cannula during the injection. Generally, the insertion distance of the cannula into the scleral layer is at least about 1.5 mm, more typically about 2-3 mm, in order to have a good hydrodynamic seal,

although the insertion distance is not limited thereto. In some embodiments, the cannula is preferably inserted into the sclera a distance that is greater than or equal to the thickness of the sclera, preferably at least one and a half times the thickness, measured at the entry point on the exterior surface. This is particularly useful near the equator where the sclera is quite thin, but is not limited to such a region. By increasing the surface area between the cannula and the scleral tissue, a better hydrodynamic seal can be formed which allows for larger and/or faster injections.

The cannula is not particularly limited and need only fit within the thickness of the sclera at the point of entry. Preferably the cannula is sufficiently small in diameter that no hole is visible in the sclera upon macroscopic observation of the entry site after the injection. Typically, at least a 25 gauge, preferably at least a 28 gauge, more preferably about 30-33 gauge cannula is employed, but such is not required. The size of the cannula depends in part on the viscosity of the material to be injected, the amount of material to be injected, and the time of injection. A very fine gauge cannula, while causing little if any trauma to the eye, may not be able to allow sufficient flow of a particular material into the sclera and thus would not serve as a useful conduit. The above gauge sizes are, especially for humans, a size that typically accommodates these competing features. Preferably the cannula is sharp on its leading end (i.e. a needle) such as with a bevel or a hollow ground point. In some cases it may be desirable that the bevel engages the sclera in an upside down orientation whereby the leading edge of the bevel is adjacent to and makes first contact with the exterior surface of the sclera. This can aid in holding the cannula in alignment with the sclera as the cannula is inserted and in preventing or reducing the risk of the cannula rotating the eye or sliding/skidding on the scleral tissue. The desirability of such an upside down bevel approach depends upon the insertion angle, the thickness of the sclera, the shape of the cannula and the size of the cannula. The aperture through which the material exists the cannula can be on the terminal end of the cannula or on the

side of the cannula. By selecting the aperture location, the general direction of the material being injected into the sclera can be controlled.

The insertion of the cannula can be carried out by hand or with a device. In a preferred embodiment of the invention, the insertion is carried out using a guided injection device. In general, a guided injection device has a mechanism for providing a
5 needle at a predetermined angle of insertion and preferably a predetermined depth of insertion. For example, a device having a guide platform which comprises a support surface that generally conforms to the shape of the sclera and a channel extending through it for guiding the needle can be advantageously employed. When the support surface is
10 contacted to the exterior surface of the sclera, the angle of the channel relative to the sclera is fixed. The needle transmitted through the channel will thus be inserted into the sclera at the predetermined insertion angle. Various mechanical means, such as a stop or collar, can be used to limit the insertion distance of the needle. The needle itself is connected to the material to be injected, such as by directly attaching to a reservoir on the
15 device or to a remote reservoir, so as to facilitate the injection step. For safety the needle is preferably retractable such that after injection of the material, the needle can be withdrawn back within the device, behind the support surface. Actuators for achieving the back and forth movement of a needle are well known in the art. Such a guide platform can be placed on the distal end of the device shown in U.S. patent 5,273,530, and thus,
20 with an appropriate predetermined angle of insertion, make the blind insertion of a needle into the sclera at the back of the eye a safe procedure.

With the cannula inserted into the sclera, the material is injected via the cannula and into the scleral layer. The rate of injection of the material via a cannula into the sclera is dependent on several factors including the viscosity of the material, the
25 duration of the injection (or the amount of material to be injected), and the desired result of the injection and can be readily determined by workers of ordinary skill in the art.

Generally, the injection rate is at least about 0.1 $\mu\text{l/s}$, typically from about 0.1 to about 8.0 $\mu\text{l/s}$, although higher rates may be preferred for some applications. For example, if the injection is intended to form a depot of material within the sclera so as to accommodate extended release of the material to the underlying tissues, then generally lower injections

5 rates are used such as from 0.1 to about 3.0 $\mu\text{l/s}$. In this way, the injected material is held in the scleral layer and diffuses out over time. Alternatively, the material can be injected into the sclera so as to leave more quickly than by simple diffusion. By injecting the material under sufficient force, at least a portion of the material can be propelled through the scleral layer. Under this approach, generally higher injection rates are used such as

10 from 2.0 to about 8.0 $\mu\text{l/s}$. However, it is possible to propel a portion of the injected material through the sclera without using high flow rates by injecting larger amounts of material than the sclera can hold. In this way the storage depot capability of the sclera is exceeded and the injected material is forced out and into the underlying tissues.

Nonetheless, usually the injection rate is within the above range and the injected material is

15 propelled through the sclera by the force of injection (i.e., the velocity obtained therefrom), only. Such higher injection forces can be used without a high risk of damage to the underlying sensitive tissues because, in part, the partial thickness of the scleral layer serves as a diffuser to slow down and somewhat disperse the injection stream. In either event, the injection conditions are such that at least a portion of the material injected into

20 the scleral layer is also propelled through the remainder of the scleral layer and into the underlying tissues (hereinafter sometimes referred to as the "propelling-type injection"). The amount of propelled material that exits the sclera varies from greater than zero to essentially all of the injected material. Typically, at least 10 %, more preferably at least about 25%, is propelled through the scleral layer and into the underlying tissues. The

25 remainder of the material will usually diffuse out of the sclera over time, although such is not required. In this way, a combination of immediate or near immediate treatment and

extended or sustained treatment can be attained by appropriately proportioning the amount of material that is propelled out of the sclera and the amount that diffuses out of the sclera. Other factors that affect the propelling/diffusing ratio include the nature and viscosity of the material, the proximity of the cannula to the interior surface of the sclera, the angle of injection and the orientation of the cannula aperture, and the amount of material injected.

In a preferred embodiment for a propelling-type injection, the cannula aperture is located on the side, generally perpendicular to the insertion direction, and oriented toward the interior surface of the sclera. In this way, the injected material is directed toward the underlying ocular tissues and is thus more likely to have sufficient propulsion from the injection to traverse the remaining scleral layer and reach these tissues.

One advantage of the propelling-type injection is the ability to force relatively large particles through the scleral layer that would not ordinarily or not readily diffuse out of the sclera. This means that proteins, viral vectors, antibodies, gene therapy constructs, etc., can be delivered to the ocular tissues in the posterior segment of the eye without penetrating the sclera and despite the fact that the materials may be too big to fit through the scleral layer. The sclera, although inelastic, will nonetheless allow these larger particles to pass through. Typically these larger particles have a particle size of at least 50 nanometers and generally are in the range of 50 to 200 nanometers, preferably 50 to 150 nanometers. In this embodiment, the hydrodynamic seal around the cannula should be taken into account along with the injection rate in order to prevent the injected material from backing out of the sclera along the sides of the cannula, as has been discussed above.

Cannular injections typically will last for up to 10 seconds, although longer injection times are possible, especially with the use of a hand rest/support, and are contemplated by the present invention.

A different embodiment of the present invention uses needle-less injection to carry out the injection of material into the cannula. Needle-less injection techniques are well known in connection with injecting into skin. In general, a solution or dry particles are driven by a forced fluid such as gas at very high velocities to the surface of the skin.

- 5 The duration of the injection is very brief, fractions of a second, so as to be considered instantaneous. At the point of contact (the site of injection), the nozzle through which the material is propelled, forms a seal with the skin. Because of the high speed, generally supersonic, the material penetrates the skin, the path of least resistance, without the aid of a needle. However, skin is relatively elastic and unlike the sclera. Accordingly, devices
- 10 commercially sold for needle-less injection into skin will generally have poor performance if used to inject into the sclera. In particular, a short burst of material directed at high speed at the sclera tends to bounce off instead of penetrate the scleral layer. Accordingly, a slower, sub-sonic approach with longer injection duration is preferred for intrascleral injection. By driving the material so as to attain sufficient momentum, but without excess
- 15 speed, the material will be more likely to penetrate into the scleral layer than bounce off. Typically the injection duration is at least one second and generally from 1 to 10 seconds, although longer times can be used. Improving the seal between the nozzle and the sclera is also beneficial to improving penetration efficiency.

- As with a cannular injection, the material injected by the needle-less
- 20 technique can form a depot within the sclera and/or a portion of the material can be propelled through the sclera and into the underlying tissues. The depth of penetration depends on the size and nature of the material, the momentum of the material, the duration of the injection and the seal between the nozzle and the sclera. Unlike the cannular propelling-type injection, needle-less injection generally can not be used to inject large
- 25 particles. It is believed that this is do in part to (1) the nature and physical dynamics of needle-less injection technology and (2) the fact that the needle-less injection technique

requires the material to be propelled the entire thickness of the sclera in order to reach the underlying tissues. In contrast, the cannular propelling-type injection propels the material from within the scleral layer and thus need only propel the material a partial thickness of the sclera; i.e. the remaining thickness from the cannular aperture to the interior surface layer. Accordingly, needle-less injection into the sclera normally uses material that has a particle size of less than about 40 nanometers and preferably 20-40 nanometers.

The entry point on the exterior surface of the sclera overlies the retina and thus is in the posterior segment of the eye. It should be noted, however, that the injection of material into the sclera may occur at a location within the sclera that does not overlie the retina, depending upon the angle and direction of injection; e.g., in the case of a cannular injection in a substantially rotational direction, the injection site within the sclera may be anterior to the retina. Nonetheless, generally, and preferably, the injection site of the material within the sclera is also over the retina.

Preferably the entry point and injection site are posterior to the area of eye muscle insertion, more preferably posterior to the equator of the eye, and more preferably more than 45 degrees posterior to the equator. Also, when a disease or condition is present or concentrated in a local area, such as macular degeneration, it is preferred to make the injection in the vicinity of the affected area. In this way, any depot of the injected material formed within the sclera is near the site to be treated while any propelled material is likely to reach the intended affected tissue. Preferably a portion of the injected material at least partially overlies the localized area to be treated. Such can allow for more effective treatment and/or reduced amounts of material needed to be injected. Also, because any material that is not propelled is stored within the sclera, the material remains in proximity with the affected area regardless of eye movement.

The posterior segment can be reached in order to make an injection in a number of ways. The eye can be rotated in order to expose the posterior segment. This is

typically accomplished by holding the conjunctiva with forceps and rotating the eye so that the front of the eye moves downwardly (i.e. "rotated forwardly"). The eye can be rotated in other directions as appropriate and other techniques for rotation can be used as desired. Another technique involves using a curved handled device that can be inserted around the eye to position the cannula, needle-less injection nozzle, or other injection apparatus over the desired posterior location. The concept of such a device is shown in U.S. patent 5,273,530. While the device could be used as shown therein, it should preferably be modified so that the cannula is retractable and more preferably modified so that the cannula will be inserted in a substantially rotational direction.

10 Accessing the posterior of an eye also normally entails penetrating the conjunctiva. One way is to make an incision in the conjunctiva and insert the cannula, nozzle, or other injection apparatus through the incision to the sclera. Such a method works with both the eye rotating technique and the curved handle device technique discussed above for accessing the posterior segment of the eye. Such an incision is
15 relatively non-invasive and is similar to conjunctival incisions (peritomy) that ophthalmologists make in carrying out other procedures. Another approach is to rotate the eye into the desired position and then inject through the conjunctiva and into the sclera. For example, in the case of a cannular injection, this means inserting the terminal end of the cannula through the conjunctival layer and into the sclera. In this approach, it
20 may be necessary to prevent movement of the conjunctiva relative to the sclera. This can be done by taking into account the relative looseness of the conjunctiva, the angle of insertion, the presence of a bevel and its orientation, and the use of conjunctiva holding or stabilizing devices or techniques. For example, holding a portion of the conjunctiva in place by physical restraint (e.g., friction or pins) while inserting the cannula can be
25 effective in preventing relative movement between the conjunctiva and the sclera. Relative

slipping between the conjunctiva and the sclera are less of a concern with needle-less injection techniques.

The material to be injected can be any material having a therapeutic or diagnostic utility or purpose. The material can be a gas, a liquid, a suspension, a colloidal suspension (particles of less than about 200 nanometers), an emulsion, a gel-sol, a powder, etc., so long as it is injectable. Preferably, the material is injectable through a cannula. Typically the materials injected in the present invention are similar to intravitreal and intramuscular injection formulations in terms of concentrations, viscosities, adjuvants, etc., although such is not required. A large number of diagnostic and therapeutic materials are well known in the art for treating various ocular diseases and conditions, as is their preparation and formulation, and all such materials are specifically contemplated for use in the present invention.

A "therapeutic material" means a material that provides a healing, restraining or prophylactic effect to a disease or condition or which suppresses, ameliorates or prevents the symptoms associated with a disease or condition. The material can be a single substance or a combination of substances. Typically, a therapeutic material is a composition containing a pharmaceutically active agent and an ophthalmically acceptable carrier or diluent. The active agent useful in the present invention include all ophthalmically effective agents, examples of which include anti-angiogenesis agents such as metalloproteinase inhibitors, vascular endothelium growth factor (VEGF) regulating agents, fibroblast growth factor (FGF) regulating agents, integrin blockers, protein kinase C inhibitors, and endogenous angiogenesis inhibitors (e.g., angiostatin); ischemic/reperfusion preventing agents such as NMDA receptor antagonists, AMPA receptor antagonists, antioxidants, peroxidation inhibitors, apoptosis inhibitors, adenosine or adenosine regulating agents, calcium channel blockers, and nitric oxide regulating agents; anti-inflammatory agents such as steroidal and non-steroidal anti-inflammatory

agents; antiviral agents; antioxidants; antibiotics; antitumor agents such as tumor necrosis factors; anti-cataract agents; anti-glaucoma agents; anesthetics; cellular regeneration agents such as telomerase; gene therapy compositions which are typically comprised of a nucleic acid and/or a protein and a vector and include triplex nucleic acids, ribozymes
5 viruses, plasmids, and liposomes; antibodies and fragments thereof; and antisense compounds.

Specific examples of useful active agents include, but are not limited to, pilocarpine, timolol, atenolol, betaxolol, levobunolol, tetracycline, hydrocortisone, prednisolone, prednisone, dexamethasone, progesterone, fluorometholone, lazarooids and
10 21-aminosteroid compounds as disclosed in U.S. Patent 5,124,154 (incorporated herein by reference), aspirin, benoxaprofen, benzofenac, bucloxic acid, butibufen, carprofen, cicloprofen, cinmetacin, clidanac, clopirac, diclofenac, etodolac, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flunoxaprofen, furaprofen, flurbiprofen, furobufen, furofenac, ibuprofen, ibufenac, indomethacin, indoprofen, isoxepac, ketorolac,
15 ketoprofen, lactorolac, lonazolac, metiazinic, mioprofen, naproxen, oxaprozin, oxepinac, phenacetin, pirprofen, pirazolac, protizinic acid, sulindac, suprofen, tiaprofenic acid, tolmetin, zomepirac, tolrestat, lisinopril, statil, retinoic acid, methotrexate, mitomycin, urokinase, streptokinase, cephaloridine, chloramphenicol, clindamycin, tobramycin, penicillin, ampicillin, erythromycin, streptomycin, neomycin, cyclosporine A, cyclosporine
20 G, TGF- β , TGF- β 2, TNF- α , TNF- β , bFGF, and α -2a interferon, anti-FGF antibody, anti-VEGF antibody, FGF antisense, VEGF antisense, VEGF receptor blockers, cysteine analogs, terilazad mesylate, angiostatin, endostatin, memantine, Cerestat, Batimastat, Marimastat, superoxide dismutase, GEM-antisense compounds, Lexipafant, nanoparticles, adeno viral vectors, adeno-associated viruses, retrovirus vectors, picorna viral vectors,
25 liposomes, cationic lipid systems and protein/nucleic acid complexes.

One advantage of the present invention is the ability to use enzyme-unstable agents. Because the sclera is avascular, enzymes that would normally attack and degrade certain proteins and other agents if placed intraocularly, will not generally reach the intrascleral depot formed by the present invention.

5 The active agent can be combined with a suitable carrier or diluent, if needed, as is well known in the art and includes aqueous as well as non-aqueous systems. The composition used in the present invention contains no physiologically or ophthalmically harmful constituents. Typically purified or deionized water is used. The pH is adjusted as needed by adding any physiologically and ophthalmically acceptable pH
10 adjusting acids, bases or buffers. Examples of acids include acetic, boric, citric, lactic, phosphoric, hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tromethamine, THAM (trishydroxymethylamino-methane), and the like. Salts and buffers would include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of
15 the aforementioned acids and bases. The pH is typically in the neutral range such as from about 6 to about 8, but is not limited thereto. Non-aqueous systems include the use of known ophthalmically acceptable oils such as polyethylene glycols and silicone oils. The active agent can be in solution, in suspension, or both. If the active agent is in solid form, its particle size should be sufficiently limited to permit injection (e.g., the agent is able to
20 pass through a cannula) and so as not to cause irritation to the eye once injected.

 In a preferred embodiment, the composition contains a component that facilitates or improves the sustained release of the active agent as is known in the art. For example, incorporating a polymeric suspending agent can provide or enhance sustained release. The polymer should be biodegradable or biocompatible such that it can be cleared
25 from the eye by natural transport effects. The active ingredient can be incorporated into the polymer matrix, adsorbed on the polymer surface, encapsulated within a polymer

coating, etc. as are well known in the art. Examples of suitable polymers include water-soluble polymers such as dextran, polyethylene glycols, polyvinylpyrrolidones, polysaccharide gels, Gelrite®, cellulosic polymers like hydroxypropyl methylcellulose and carboxymethylcellulose, hyaluronic acid polymers, and poly(lactic acid) and copolymers of lactic acid and one or more of glycolic acid, malic acid, glyceric acid, and tartaric acid. Carboxy-containing polymers such as uncrosslinked polyacrylic acids and copolymers thereof are also useful as suspending agents for insuring sustained release. Crosslinking is permissible only to the extent that the polymer can clear; i.e., crosslinking generally prevents biodegradation and thus the entire polymer must be susceptible of being cleared from the eye. Other forms include liposomes and lipid emulsions.

The composition should contain a sufficient amount of active ingredient to achieve the desired effect as can be readily determined by workers skilled in the art. In general, the solubility of the active ingredient in water and the concentration of the active ingredient needed in the tissue, guide the amount and rate of release of the agent. It should be borne in mind that the sclera is a depot of limited size and the concentration of the agent may need to reflect this. In general the amount of material to be injected is at least 0.1 μ l, typically from around 0.1 to 25 μ l, more typically from about 1 to 25 μ l, such as from about 3 to about 25 μ l or from about 3 to 10 μ l. If more material is needed then can be practically delivered in a single injection, then multiple injections can be performed; i.e., injecting 6 μ l of therapeutic material in three different sites within the sclera during a single office visit.

Other components of the therapeutic material include solubilizers, stabilizers, preservatives, and other ingredients as are well known in the ophthalmology art. If the composition is supplied as a ready to inject single dose, then a preservative is typically omitted. The composition can be provided as a frozen liquid or as a lyophilized powder for reconstituting.

Diagnostic materials include gases and dye solutions. For example, a gas such as nitrogen, air, or other inert gas, can be supplied in order to inflate the area and aid in some types of diagnostic procedures; i.e., improving the image in an ophthalmoscope. Similarly, a dye can be injected in order to aid in diagnosing various conditions by

5 providing higher contrast and/or a staining pattern.

The present invention can be used to treat a variety of ocular diseases or conditions including, but not limited to, cystoid macular edema, age-related macular degeneration, diabetic retinopathy, diabetic maculopathy, central retinal artery occlusion, central retinal vein occlusion, branch retinal artery occlusion, branch retinal vein occlusion,

10 retinopathy of prematurity, sickle cell retinopathy, photic retinopathy, radiation retinopathy, retinal detachment, retinitis pigmentosa, macular hole, cataract, and glaucoma as well as accidental or surgically induced trauma to the eye. Suitable therapeutic materials, known for treatment of an ocular disease or condition, especially a retinal disease or condition, can be injected into the sclera in close proximity to the affected site

15 by the present invention to thereby provide effective treatment and enhanced delivery.

For example, one embodiment of the invention relates to treating neovascular diseases of the eye, such as diabetic retinopathy, macular degeneration, and neovascularization of the retina or choroid, by injecting into the sclera, through a location on the exterior surface of the sclera that overlies retinal tissue, an effective

20 neovascularization reducing or preventing amount of an anti-angiogenesis agent. Such agents are described above and are generally well known in the art, including metalloproteinase inhibitors, vascular endothelium growth factor regulating agents, FGF regulating agents, integrin blockers, and protein kinase C inhibitors. The VEGF regulating agents include, without limitation, VEGF, antisense compounds thereof,

25 antibodies thereof, and antibody fragments thereof having anti-angiogenesis activity.

Antioxidants are also a highly useful class of compounds for treating these types of diseases.

With regard to macular degeneration, it is preferred that the insertion site is over the macula or in its immediate vicinity (e.g., more than 45 degrees posterior to the equator). More preferably, the insertion and injection steps provide at least a portion of the intrasclerally injected therapeutic material overlying the macula. The material to be injected can be any macular degeneration treating material. The "macular degeneration treating material" embraces substances that seek to relieve the symptoms of the disease, counteract the cause(s) of the disease or offset the disease by regenerating cells.

Specifically contemplated active agents include the above anti-angiogenesis compounds of VEGF, an antisense compound of VEGF, an antibody of VEGF, a fragment of an antibody of VEGF, triplex nucleic acids of VEGF, a receptor blocker for VEGF, ribozymes for VEGF, telomerase, genes encoding for telomerase, and gene therapy vectors including nanoparticles, adeno viral vectors, adeno-associated viruses, retrovirus vectors, picorna viral vectors, liposomes, cationic lipid systems and protein/nucleic acid complexes, as well as antioxidants.

Another embodiment is treating cataracts. Although the disease manifests in the anterior segment, its root cause may lie in the posterior segment. Providing an antioxidant into the posterior segment can prevent or reduce cataracts. Here a preferred antioxidant is a 21-aminosteroid such as a lazaroid.

The following examples serve to illustrate the materials that can be injected by the present invention and should not be considered to limit the scope of the present invention.

25

Example 1

An injectable therapeutic material containing the PAF antagonist Lexipafant (BB-882) is prepared as follows. In a 250-ml beaker, about 50 g of DI water

is added and heated up to 80-90°C on a hot plate while stirring with a magnetic stir bar. HPMC is dispersed into the hot water and stirred for 15 min. followed by cooling to RT while stirring. 10 g of room temperature water is then added to the polymer and stirred for 10 min. In a separate container, Pluronic F-127 and sorbitol are dissolved in 20 g of DI water. Glycerin is then added to the Pluronic F-127 solution and stirred until dissolve completely. The Pluronic F-127 solution is then added to the polymer suspension and stirred for 10 min. BB-882, dissolved in 1N HCl solution, is then added to the polymer mixture with stirring for 10 min. The pH of the resulting polymer mixture is adjusted to about 7.4 with 2N NaOH, stirred for 10 min., and then brought to 100% with q.s. of DI water. The formulation may be made sterile by heating the formulation to 123°C for 30 minutes and sterile filtering the drug, NaOH, and residual water after heating. The 100 grams of material is summarized in the following table:

COMPOSITION	% (Wt/Wt)
BB-882	1.0
Hydroxylpropyl Methylcellulose, Type 2910, USP	2.5
Sorbitol, USP	1.5
Glycerin, USP	1.0
Pluronic F-127, NF	1.0
Hydrochloric Acid, (1N solution)	5.0
Sodium Hydroxide, NF, 2N for pH adjustment	q.s. to pH 7.4
Purified Water, USP	q.s.

15 Total weight: 100 grams

Example 2

In a manner similarly to that set forth in Example 1, the following materials
20 can also be made:

COMPOSITION	% (Wt/Wt)
BB-882	0.1
Hydroxylpropyl Methylcellulose, Type 2910, USP	2.5
Sorbitol, USP	1.5
Glycerin, USP	0.2
Edetate Disodium, USP	0.10
Sodium Chloride, USP	0.32
Sodium Hydroxide, NF, 2N for pH adjustment	q.s. to pH 6
Purified Water, USP	q.s.

Total weight: 100 grams

5 Example 3

In a manner similarly to that set forth in Example 1, the following materials can also be made:

COMPOSITION	% (Wt/Wt)
Diclofenac Na, USP	0.1-1.0
Hydroxylpropyl Methylcellulose, Type 2910, USP	2.5
Mannitol, USP	1.5
Sodium Chloride, USP	0.21
Poloxamer 407, NF	0.05
Boric Acid, USP	0.5
Magnesium Chloride, USP	0.05
Sodium Hydroxide, NF, 2N for pH adjustment	q.s. to pH 6
Purified Water, USP	q.s.

10

Total weight: 100 grams

Example 4

Lazaroids are known to be potentially useful in treating a variety of ocular ischemic diseases such as glaucoma and diabetic retinopathy. Suitable formulations may be generally formulated as follows. 0.005 grams of the aminosteroid is dissolved into a saline solution formed of 0.9 grams of sodium chloride dissolved in intravenous grade water. The pH is then adjusted to 7.4 with NaOH and the total weight adjusted with

water to 100 grams. The mixture is then sterilized. Alternatively, if the aminosteroid is not a powder, but is a lipid emulsion or in a liposome, it can be dispersed in the saline solution. A suspension can be made by adding hyaluronic acid such as sodium hyaluronate, or other suitable polymer, typically about 1.0 grams and with an increase in
5 the amount of the agent, such as to 0.05 grams. The suspension need only remain sufficiently viscous to allow injection. Suitable aminosteroids include U-74006F, U-74500A, and U-75412A.

Another formulation is to slowly add 10 grams of U-74006F to 950 ml of pure water having 20 millimoles of citric acid under an inert atmosphere and with stirring.
10 Three millimoles of sodium citrate and 8 millimoles of sodium chloride are added with stirring until a clear solution is obtained. The solution can then be sterilized.

Example 5

An injectable therapeutic material containing Batimastat (BB-94) is
15 prepared as follows. In a 250-ml beaker, about 50 g of DI water is added and heated up to 80-90°C on a hot plate while stirring with a magnetic stir bar. HPMC is dispersed into the hot water and stirred for 15 min. followed by cooling to RT while stirring. 10 g of room temperature water is then added to the polymer and stirred for 10 min. In a separate container, Pluronic F-127 and sorbitol are dissolved in 20 g of DI water. Glycerin is then
20 added to the Pluronic F-127 solution and stirred until dissolve completely. The Pluronic F-127 solution is then added to the polymer suspension and stirred for 10 min. BB-94 is then added to the polymer mixture with stirring for 10 min. The pH of the resulting polymer mixture is adjusted to about 6.0 with 2N NaOH, stirred for 10 min., and then brought to 100% with q.s. of DI water. The formulation may be made sterile by heating

the formulation to 123°C for 30 minutes and sterile filtering the drug, NaOH, and residual water after heating. The 100 grams of material is summarized in the following table:

COMPOSITION	% (Wt/Wt)
BB-94	0.3
Hydroxylpropyl Methylcellulose, Type 2910, USP	2.5
Sorbitol, USP	1.5
Glycerin, USP	1.0
Pluronic F-127, NF	1.0
Sodium Hydroxide, NF, 2N for pH adjustment	q.s. to pH 6.0
Purified Water, USP	q.s.

Total weight: 100 grams

5

Example 6

An injectable Adeno virus vector (AVV) at a titer of 1 to 5×10^5 /ml in phosphate buffered saline is prepared as follows. The AVV is prepared by diluting a concentrated solution of virus using phosphate buffered saline, pH 7.0, such that 20 microliters contains a multiplicity of infection of 0.2 to 0.6 virus particles/pigmented retinal epithelial cell.

The invention having been thus described, it will be obvious that the same may be varied in many ways without departing from the scope and spirit of the invention as defined by the following claims.

15

We claim:

1. A method of intrascleral injection, which comprises:
injecting into the scleral layer of an eye through a location on the exterior surface of the sclera that overlies retinal tissue an effective amount of a therapeutic or diagnostic material.
2. The method according to claim 1, wherein the amount of material injected is at least 0.1 μ l.
3. The method according to claim 1, wherein the material comprises a pharmaceutically active agent and an ophthalmically acceptable carrier.
4. The method according to claim 3, wherein said ophthalmically acceptable carrier is water or oil.
5. The method according to claim 3, wherein said pharmaceutically active agent is selected from the group consisting of metalloproteinase inhibitors, vascular endothelium growth factor regulating agents, fibroblast growth factor regulating agents, integrin blockers, protein kinase C inhibitors, endogenous angiogenesis inhibitors, calcium channel blockers, NMDA receptor antagonists, AMPA receptor antagonists, antioxidants, peroxidation inhibitors, apoptosis inhibitors, adenosine or adenosine regulating agents, nitric oxide regulating agents, anti-inflammatory agents, antiviral agents, antibiotics; antitumor agents, anti-cataract agents, anti-glaucoma agents, anesthetics, antibodies and fragments thereof, antisense compounds, ribozymes, and triplex nucleic acids.

6. The method according to claim 3, wherein said material further comprises a biodegradable polymer matrix.
7. The method according to claim 1, wherein said injection is made posteriorly to the equator of the eye.
8. The method according to claim 7, wherein said location on the exterior of the sclera through which said injection is made substantially overlies the macula or its immediate vicinity.
9. The method according to claim 1, which further comprises inserting a cannula into said sclera and carrying out said injecting step by transmitting said material through the cannula into said scleral layer.
10. The method according to claim 9, wherein said cannula is inserted into said scleral layer in a substantially rotational direction.
11. The method according to claim 9, wherein said cannula is inserted into said scleral layer a distance greater than the thickness of the sclera at the location of insertion.
12. The method according to claim 9, wherein said insertion is carried out using a guided injection device.
13. The method according to claim 9, wherein said cannula is inserted at an insertion angle of less than about 60 degrees.

14. The method according to claim 13, wherein said cannula is inserted at an insertion angle of from about 20 to 40 degrees.

15. The method according to claim 9, wherein said cannula is inserted in a fail safe orientation.

16. The method according to claim 9, wherein the material is injected at a rate of from about 0.1 to about 3.0 $\mu\text{L/s}$.

17. The method according to claim 16, wherein the amount of material injected is within the range of about 3 to about 25 μL .

18. The process according to claim 9, wherein said material is injected into said scleral layer under sufficient force that at least a portion of said material is propelled through said scleral layer.

19. The method according to claim 18, wherein the material is injected at a rate of at least 4 $\mu\text{L/s}$.

20. The method according to claim 18, wherein said material comprises a colloidal suspension.

21. The method according to claim 20, wherein said colloidal suspension comprises particles ranging in size from 50 to about 150 nanometers.

22. The method according to claim 9, further comprising, making an incision in a conjunctival layer and passing said cannula through said incision, prior to said insertion step into the scleral layer.
23. The method according to claim 1, wherein said material is injected into said scleral layer by needle-less injection.
24. The method according to claim 23, wherein said material is accelerated so as to impact said location on the exterior surface of the sclera at sub-sonic speeds.
25. The method according to claim 23, wherein said material is a liquid or a particulate suspension whose particles are not more than about 40 nanometers.
26. The method according to claim 23, wherein a portion of said material is conveyed into and through said scleral layer.
27. The method according to claim 26, wherein a majority of said material is conveyed into, through and out the interior surface of said scleral layer.
28. The method according to claim 1, further comprising repeating said injecting step through one or more locations on said scleral layer.
29. The method according to claim 1, wherein said eye is suffering from an ocular disease and said material is a therapeutic material effective for treating said disease.
30. The method according to claim 29, wherein said disease is selected from the group consisting of cystoid macular edema, age-related macular degeneration, diabetic

retinopathy, diabetic maculopathy, central retinal artery occlusion, central retinal vein occlusion, branch retinal artery occlusion, branch retinal vein occlusion, retinopathy of prematurity, sickle cell retinopathy, photic retinopathy, radiation retinopathy, retinal detachment, retinitis pigmentosa, macular hole, cataract, and glaucoma.

31. The method according to claim 30, wherein said disease is diabetic retinopathy and said therapeutic material comprises an anti-angiogenesis agent.

32. The method according to claim 30, wherein said disease is glaucoma.

33. A method for treating posterior ocular tissue, which comprises:
forming a depot of a therapeutic material within the sclera of an eye at a location that overlies retinal tissue, wherein said therapeutic material diffuses over time through said sclera and into the underlying tissue or tissues in an effective amount.

34. A method for treating ocular tissue, which comprises:
propelling a diagnostic or therapeutic material through at least a portion of a scleral layer and into at least the underlying choroidal or retinal tissue.

35. The method according to claim 34, which further comprises inserting a cannula through a location on the exterior surface of the sclera that overlies retinal tissue into the scleral layer and injecting said material through said cannula and into said scleral layer with sufficient force that a portion of said material is propelled the remainder of the way through said scleral layer and onto the underlying choroidal or retinal layers.

36. A method for treating macular degeneration, which comprises injecting an effective macular degeneration treating amount of a macular degeneration treating material into the sclera of an eye in need of treatment thereof through a location on the exterior surface of the sclera that overlies retinal tissue.

37. The method according to claim 36, wherein said macular degeneration treating material is selected from the group consisting of antisense compounds of VEGF, antibodies of VEGF, a fragment of an antibody of VEGF, triplex nucleic acids of VEGF, receptor blockers for VEGF, ribozymes for VEGF, telomerase, genes encoding for telomerase, nanoparticles, adeno viral vectors, adeno-associated viruses, retrovirus vectors, picorna viral vectors, liposomes, cationic lipid systems and protein/nucleic acid complexes, and antioxidants.

38. The method according to claim 36, wherein said agent is injected into a portion of the sclera that substantially overlies the macula or its immediate vicinity.

39. A method for treating a condition in the eye involving neovascularization, which comprises injecting into the sclera, through a location on the exterior surface of the sclera that overlies retinal tissue, an effective neovascularization reducing or preventing amount of an anti-angiogenesis agent.

40. The method according to claim 39, wherein said agent is selected from the group consisting of metalloproteinase inhibitors, VEGF regulating agents, FGF regulating agents, integrin blockers, and protein kinase C inhibitors.

41. The method according to claim 39, wherein said condition is diabetic retinopathy.

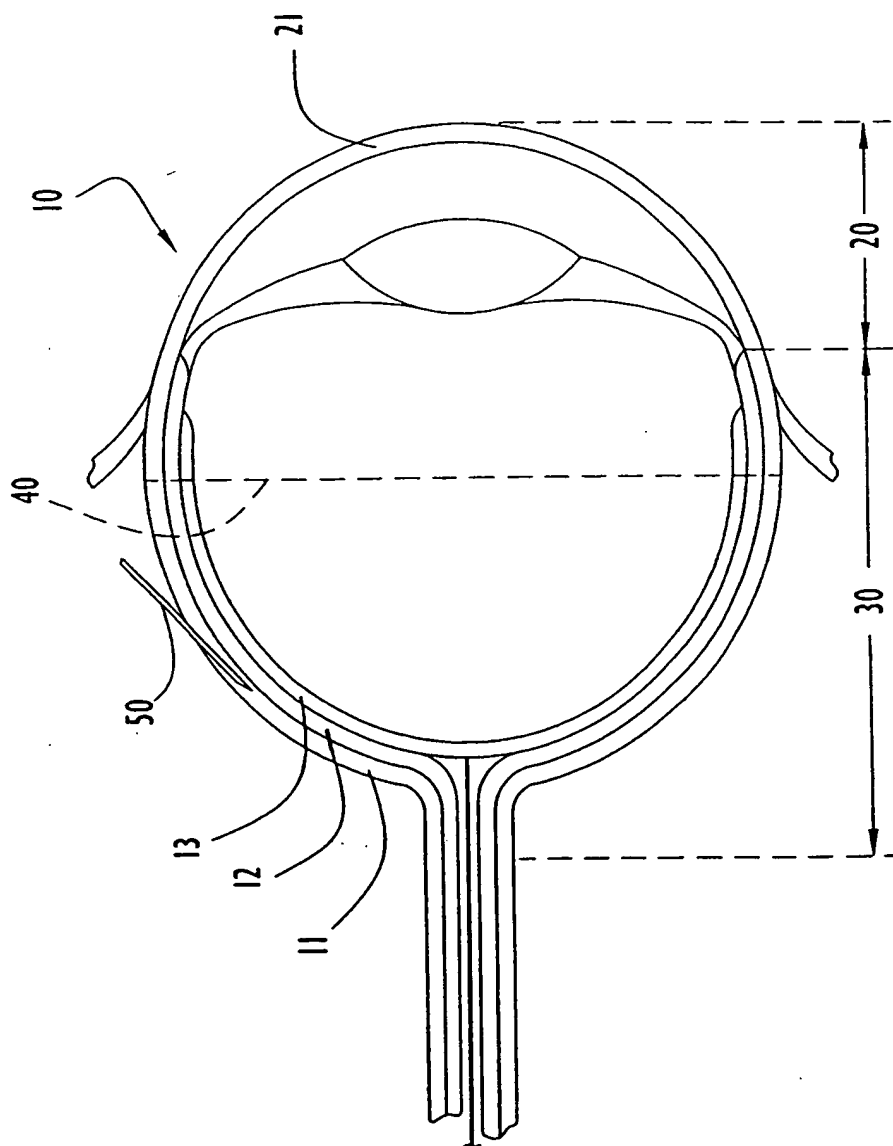


FIG. 1

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